**Case 4: Common Variable Immunodeficiency**

**Case Details**

* Past History
  + Recurrent respiratory and GI infections
  + Frequent otitis, sinusitis, tonsillitis, and intermittent diarrhea
  + At 25 yrs of age, diagnosed with thyroid insufficiency
* Physical Examination
  + Enlarged spleen
  + Lower than normal levels of all Ig isotypes
  + Immunized several times but with no Ab formation
  + Normal B and T cells
  + High levels of antithyroid antibodies
* Family History
  + Twin sister and mother had hypogammaglobulinemia and inability to make specific Abs
  + Sister – recurrent viral and bacterial infections
    - Developed hemolytic anemia and vasculitis
    - Died from GI cancer
  + Mother – Died from non-Hodgkin’s lymphoma
  + Brother – Diagnosed with CVID
* Plan of Action
  + DIAG of CVID (common variable immune deficiency)
  + Placed on IVIg 35 g every 2 weeks

**CVID (Common Variable Immunodeficiency) multiple genetic bases but this one is involved in isotype switching**

* Characteristics
  + Low serum levels of all switched Ig isotypes
  + Impaired ability to produce specific Abs, even IgM class
  + Increased susceptibility to respiratory and GI infections (IgG and A)
    - especially encapsulated bacteria
  + Severely deficient in plasma cells
  + Impaired somatic hypermutation
  + 300 fold increased risk of lymphoma and 50x risk of gastric carcinoma
  + granulomas
* Inheritance
  + Most are sporadic
  + Initially may present with IgA deficiency, which over several years may develop into CVID
  + Genetic Basis is largely unknown
    - TACI – variable penetrance, most common frequency (this case)
    - BAFF-R – arrest B-cell in an immature transitional stage
    - CD19 + CD20
    - ICOS – a co-stim molecule that is important in T to B cell cooperation
    - Msh5 – may be involved in class isotype switching

**Objectives**

* **Contrast properties of thymus-independent TI-1 and TI-2 antigens, and describe the main immunoglobulin isotype that is produced in response to these antigens.** 
  + Tl-1 – Directly induces B-cell division without T-cell help
  + Tl-2 – Probably stimulate B-cell by cross-linking B-cell receptors. It also can induce IgM and some class-switching responses
  + Both are effective in fighting encapsulated bacteria
* **Describe how the TNF/TNFR family members BAFF (B cell activating factor belonging to the TNF family) and APRIL (a proliferation-inducing TNF ligand) can replace the requirement for T cell interaction by allowing B cells to undergo some isotype switching in response to TI-2 antigens. Explain that both BAFF and APRIL appear to act via TACI, a receptor on B cells.**
  + BAFF
    - Secreted in follicles of peripheral lymphoid tissue and can bind to several B-cell protein receptors (BAFF-R)
    - Involved in B-cell development and mature B-cell survival
  + APRIL
    - Involved in proliferation of cells
    - Has no effect on B-cell development and survival
    - It binds to TACI and BCMA, not BAFF-R
  + TACI receptor
    - The one that mediates isotype switching by BAFF and APRIL
    - May also promote plasma-cell differentiation and survival
* **Explain CVID may be caused in several different ways, including some cases that are linked to a mutation in *TACI*.**
  + CVID is a “phenotype” by the previously mentioned characteristics
  + Impairing TACI would impair B-cell differentiation and will hinder isotype switching
* **Explain CVID is characterized by low levels of IgA, IgG, and IgE, a poor ability to mount antibody responses that involve isotype switching, and by significantly enhanced susceptibility to infections, including both respiratory (where IgG and IgA antibodies protect) and gastrointestinal infections (where IgA antibodies are important).**
* **List the enhanced risks of developing autoimmune diseases, lymphoma, and gastric carcinoma as major concerns for patients with CVID.**
  + Greater risk of developing autoimmune disease
  + 300x – lymphoma
  + 50x – gastric carcinoma